Hepatitis C Virus

- Virology
- Pathophysiology
- Natural History

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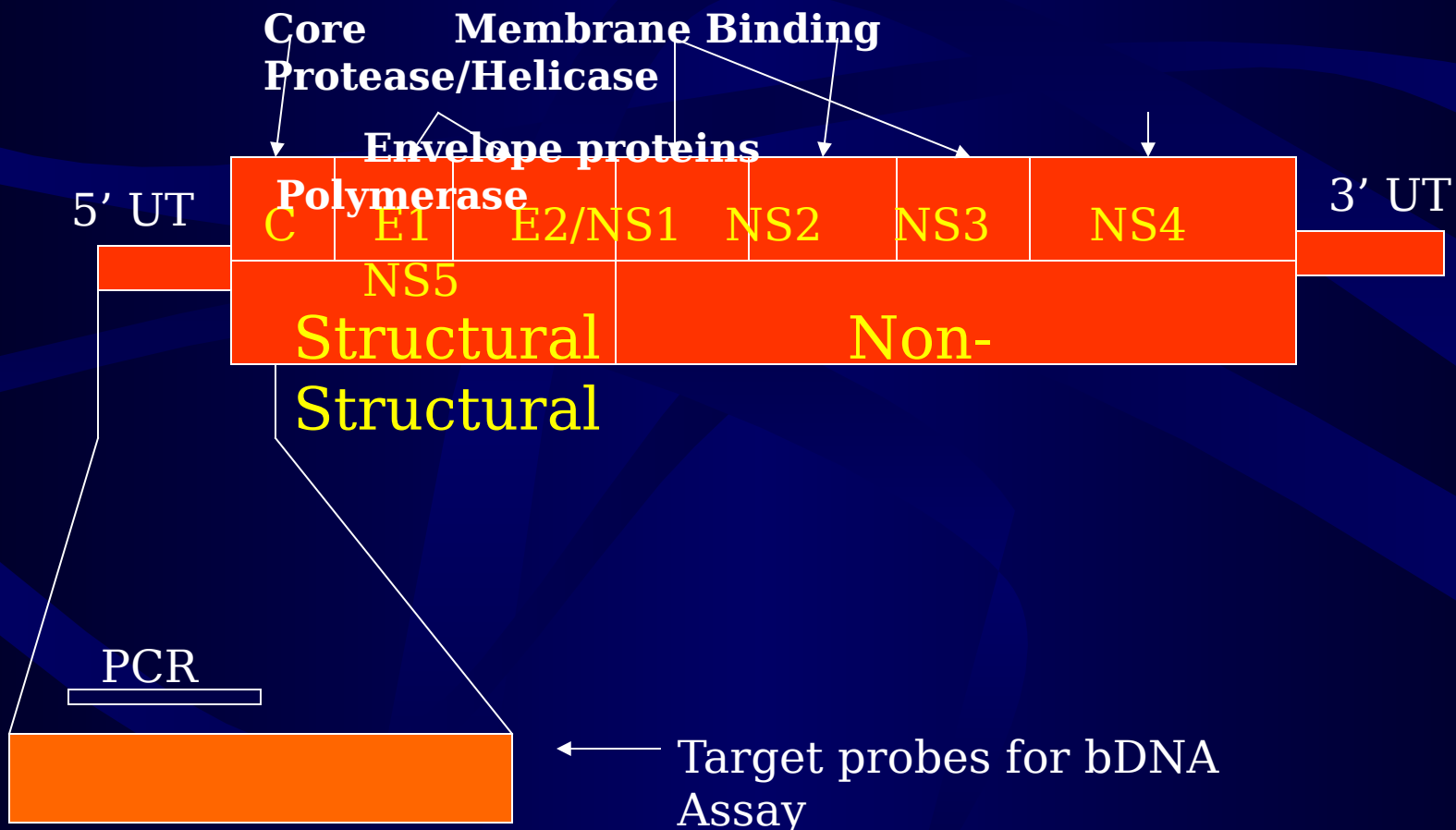
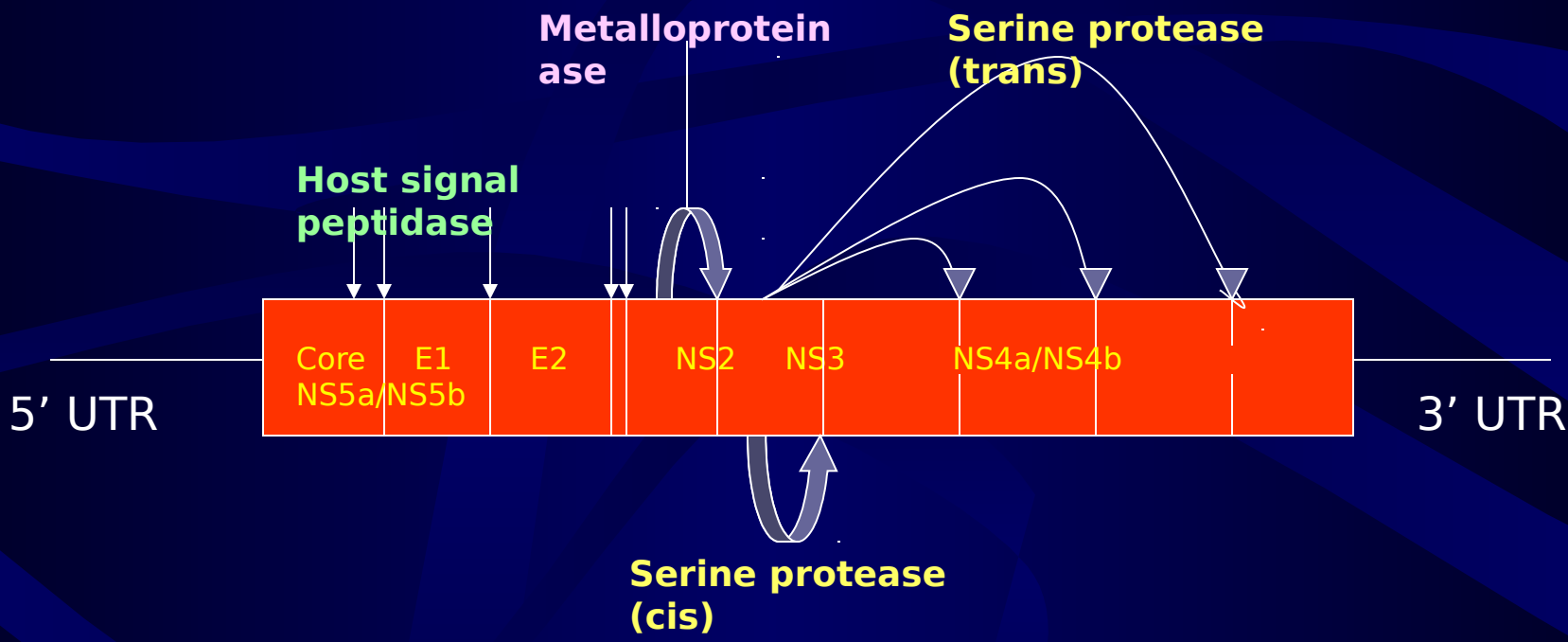
History

- *Beeson 1943*: First report of an association between blood transfusion and hepatitis. JAMA
- *Krugman 1967*: Transmissibility of hepatitis by human plasma, “serum hepatitis.” JAMA
- *Prince 1974*: Non-A, non-B hepatitis recognized as an entity. Lancet
- *Kuo 1989*: Establishment of an assay and the entire viral genome. Science

HCV Genome *Encoding regions & functions*

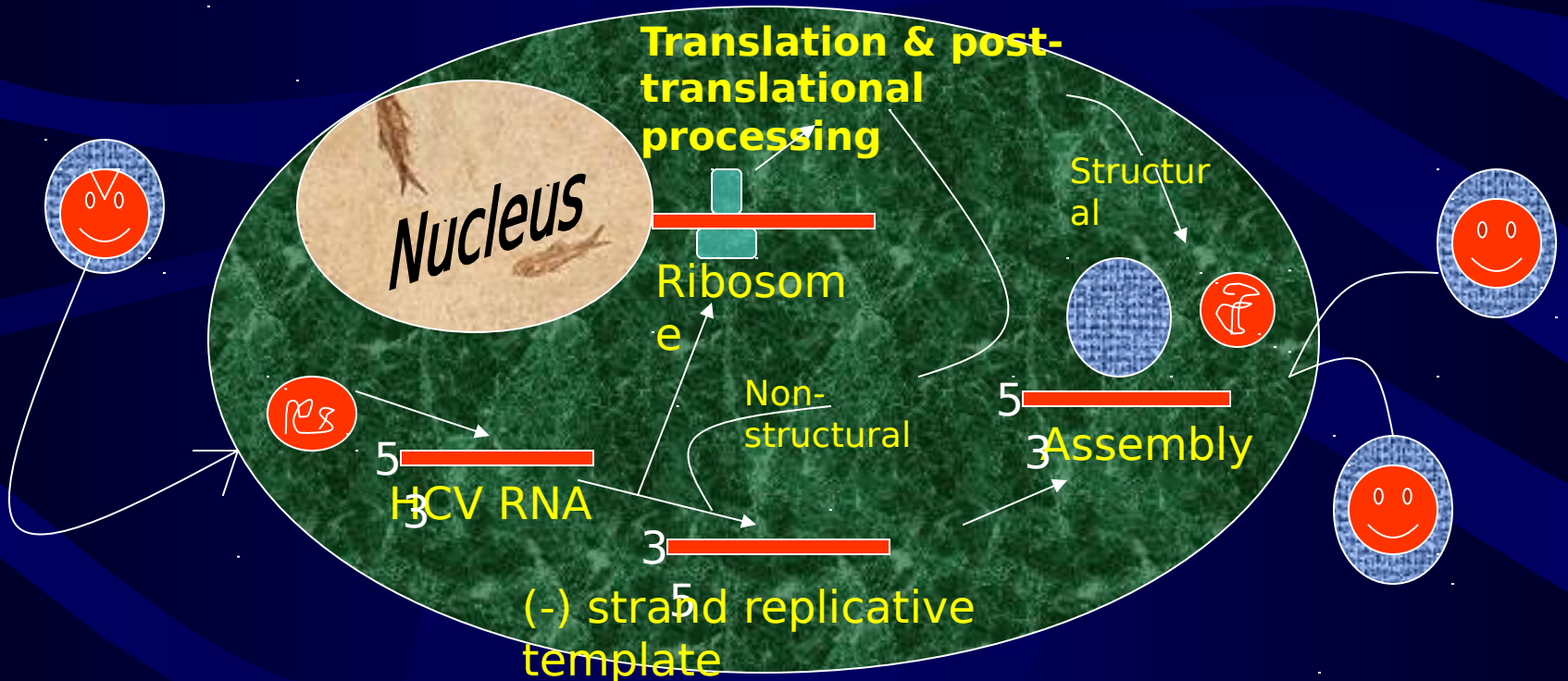


HCV Genome
Enzymatic cleavage sites



Cheney is my idol

Intracellular replication cycle



Genetic Heterogeneity

- During HCV replication, the viral RNA polymerase introduces random nucleotide errors.
- HCV is a very heterogeneous virus, with only ~70% homology among all isolates.
- Different isolates of HCV have been classified by their nucleotide variability into genotypes or subtypes.

Genetic Heterogeneity

- A consensus system for HCV nomenclature proposed by Simmonds et al. is now widely accepted.
- At least six known genotypes and more than 80 subtypes.
- Geographic differences in genotype distribution.
- Quasispecies

Pathogenesis of Liver Disease

- Host factors: - Competence of immune system - Cytokine production - Humoral & Cellular responses
- Viral factors: - Replication efficiency - Genotype & diversity - Immunoreactivity of virus - Direct injury
- Environment: - **Alcohol**

Pathogenesis Immune-Mediated Mechanisms

- Humoral Immune Response:
  - Antibodies to HCV peptides form the basis of current diagnostic assays.
  - Viral neutralization.
  - Expansion of CD-5 positive B lymphocytes.
  - Deposition of immune complexes (IgG, RF).
  - Antibody response and clinical course.
    - Anti-NS4
    - Core specific IgM

Pathogenesis Immune-Mediated Mechanisms

- Cellular Immune Response:
  - CD4+ T-Lymphocyte Response.
    - Early control of infection and protects against subsequent hepatocellular damage.
  - CD8+ T-Lymphocyte Response.
    - Control of viral replication and promotion of hepatocellular damage in chronic HCV infection.
  - Cytokine Response.
    - **Th1** cytokine response and **Th2** cytokine response.

Pathogenesis
Direct Viral Cytopathicity

- Is HCV cytopathic to liver cells?
  - Other Flaviviridae virus' are cytopathic.
  - Dying hepatocytes w/out adjacent inflam.
  - Serum aminotransferase levels and hepatic inflammation decline in relative parallel to viral levels during IFN treatment.
  - Correlation b/w serum HCV-RNA levels and the degree of hepatocellular damage.

Pathogenesis
Direct Viral Cytopathicity

- Maybe HCV is not directly cytopathic:
  - Histological markers of disease activity don’t correlate w/ serum viral levels or the amnt of HCV RNA or antigen in the liver.
  - Many patients w/ HCV infection have persistently normal serum ALT levels and minimal liver injury despite presence of detectable HCV RNA in serum.

Natural History

- Minimal requirement for study design:
  - Must be able to determine disease onset.
  - Full spectrum of acute illness identifiable.
  - Can construct a matched control group
  - Evaluation performed w/out treatment.
  - Continuous evaluation to disease endpoints.

Natural History

- The onset of HCV is rarely recognized because symptoms fail to develop in 70%.
- Since the acute HCV cases can’t always be identified, a matched control group can’t be selected.
- Conducting studies on untreated patients becoming difficult.
- Outcome study of a dz over 3-4 decades??

Natural History

- Kiyosawa and colleagues in Japan:
  - Studied 231 pts w/ chronic NANB hepatitis
  - anti-HCV found in…
    - 89.6% of the 96 w/ histologic chronic hepatitis.
    - 86.4% of the 81 w/ cirrhosis
    - 94.4% of the 54 w/ hepatocellular carcinoma.
  - Time to develop chronic hepatitis = 10yrs, cirrhosis = 21.2yrs, and HCC = 29yrs.

Natural History

- Tong et al from United States:
  - 131 pts referred for elevated ALT, established chronic liver dz, or presence of a liver mass.
  - Upon first evaluation:
    - 67.2% c/o fatigue 67.9% had hepatomegaly.
  - On liver biopsy:
    - 20.6% = chronic hepatitis 22.9% = chronic active hepatitis 51% = cirrhosis 5.3% = HCC.
  - 13.7yrs = chronic hepatitis, 20.6 yrs = cirrhosis, 28.3yrs = HCC.

Prospective studies of transfusion associated NANB hepatitis followed from onset of acute disease

Author	#pts	Mean F/U	Clinical Symp.	Cirrhosis	HCC	Liver Death
DiBisceglie	39	9.7yrs	12.8%	20%	0%	6.0%
Hopf	86	8.0yrs	4.7%	24%	NR	NR
Koretz	80	14yrs	10%	18-20%	1.3	2.5
Mattson	66	13yrs	11.5%	8-11%	NR	1.6%
Tremolada	135	7.6yrs	3.7	15.6	0.7	3.6

Retrospective studies of outcomes of chronic HCV in patients with established chronic liver dz

Author	#pts	Mean F/U	Clinical symp.	Cirrhosis	HCC	Liver Death
Takahshi	100	11 yrs	NR	42 %	19 %	NR
Yano	155	8.7	NR	30 %	15 %	NR
Tong	131	4.0 yrs	>67 %	46 %	10 %	15 %

Retrospective-Prospective Studies

- Among 53,178 recipients of anti-D immunoglobulin in the early ‘70s…
  - 417 (0.8%) were later found to be anti-HCV +
    - 232 assessed 17 years postinoculation.
    - Mean age 44.9 years
    - Mild fatigue in 26.5% as only clinical finding.
    - ALT was normal in 37.6%, b/w 40-100 IU in 52.4% and exceeded 100 IU in 10%.

Retrospective-Prospective Studies

- Liver biopsies revealed:
  - mild chronic hepatitis 55%
  - mild to moderate chronic hepatitis in 38%
  - severe chronic hepatitis in 6.8%
  - severe fibrosis in 1.8%
  - nodules with bridging fibrosis consistent with early cirrhosis in 2.4%

Retrospective-Prospective Studies

- 2,533 women in Germany received anti-D immunoglobulin b/w 1978 and 1979.
  - 160 found to be anti-HCV positive.
  - 74 recovered completely (low titers at onset).
  - 86 (54%) developed chronic hepatitis (high titers initially, and most remained elevated).

Retrospective-Prospective Studies

- National Heart, Lung, and Blood Institute Study of Transfusion-Associated Non-A, Non-B Hepatitis.
  - Follow-up evaluation of people who had developed transfusion-associated NANB hepatitis between 1968 and 1980.
  - Transfusion recipients were monitored with serum enzymes (ALT) to detect onset of acute hepatitis.

- Between 8% and 18% of recipients developed non-A, non-B hepatitis.
- Over 2/3’s did not have any symptoms.
- 568 cases w/ dx of non-A, non-B hepatitis.
- Matched transfusion control group of 984 people who did not develop hepatitis.
- Goal: to determine and compare the mortality rates, both all-cause and liver-related, as well as the hepatitis-associated morbidity b/w hepatitis cases and controls.

Mortality of transfusion-associated NANB hepatitis

DISEASE CHARACTERISTIC AND INTERVAL AFTER TRANSFUSION	*CASES (%)*	*CONTROLS (%)*	*P-VALUE*
NANB, all-cause @ 18 yrs	51	51	NS
NANB, all-cause @ 20 yrs	59	61	NS
HCV, all-cause @ 18 yrs	51	54	NS
NANB, liver-related @ 18 years.	3.2	1.5	0.033

Morbidity

- 205 cases and 492 controls.
- 30% cases & 25% controls c/o fatigue.
- Hepatomegaly only physical sign.
- Anti-HCV was detected in 70% of cases.
  - 50% with chronic hepatitis (pos. anti-HCV & RNA).
  - 20% with normal ALT (positive anti-HCV & RNA).
  - 17% only positive for anti-HCV.
  - Remaining w/out evidence of original infection.

- Among the 30% of cases whose initial acute illness samples tested negative for anti-HCV, as well as hepatitis A and B markers:
  - 5% on follow-up found to be anti-HCV and HCV RNA positive but with normal ALT.
  - 2% were anti-HCV positive only.
  - 93% were negative for all HCV markers.
    - 20% had biochemical evidence of chronic hepatitis of undefined origin (a different hepatitis virus?).

- Liver biopsies performed only on those with raised serum enzymes.
  - Chronic hepatitis……..58%
  - Cirrhosis……..33%
- Overt *clinical* evidence of chronic liver dz.
  - 5% of those with histologic chronic hepatitis alone, none with features of severe disease.
  - 70% of those with histologic cirrhosis.
    - 43% displaying evident hepatic decompensation.

Results of NHLBI study

- Both liver-related death and liver-related morbidity occur w/ only modest frequency.
- Morbidity is highest in those with cirrhosis.
- Mortality among persons w/ HCV-related compensated cirrhosis is moderate until first episode of decompensation occurs.

Mortality in compensated cirrhosis associated with chronic HCV

Probability of survival at	**%**
Three years	96
Five years	91
Ten years	79
After episode of decompensation	
Five years	50

Retrospective f/u study of 384 pts. Gastroenterology 112:463-472. 1997

In the beginning...

- **Increase in LAEs 2-26 wks after exposure.**
- Mean incubation period 7-8 wks " ".
- **HCV-RNA appears in blood within few days.**
- Anti-HCV detectable after 5-6 wks.
- **Symptoms occur in less than 30%, usually mild.**
- Fulminate hepatic failure extremely uncommon.
- **Chronic hepatitis w/ viremia and elevated ALT develops in at least 60-70% of the cases.**

What's going to happen...

- **Most pts with chronic hepatitis have asymptomatic elevations in LAEs and don't have symptomatic liver dz.**
- Only ~ 6% of pts have symptomatic liver dz.
- **~ 30% of pts infected with HCV have nl LAEs**
- Transient ALT increases occur and correlate with increases in HCV RNA but are not associated with viral clearance.
- **Correlation of symptoms and histologic severity of disease in individual patients is poor.**
- Normalization of liver tests after acute infection does not always represent resolution of infection

What can happen...

- **Level of HCV RNA correlates poorly with histology.**
- Slow rate of progression w/ during the first one to two decades.
- **Mean duration of infection before dev't of cirrhosis is ~21 yrs.**
- Compensated cirrhosis = annual risk decompensation is 3.9%.
- **Elevated PT = 39% reduction in 10yr survival.**
- Inc bili, low alb, low plts = 16-19% dec in 10yr surv.
- **Annual risk of HCC is 1.4% in US cirrhotic pts.**
- Mean duration of infection in HCC pts is ~ 29 yrs.

Factors important in the evolution cirrhosis in hepatitis C.

- Progression of disease
  - Risk highest in those with severe (grade 4/stage 3) chronic hepatitis on biopsy.
- Age at time of exposure.
  - Rate of progression more rapid if HCV acquired above the age of 50-55 years.
- Dual Infections.
  - HCV and HIV = more rapid progression of disease.

Factors important in the evolution cirrhosis in hepatitis C.

- Liver histology not more severe in pts infected with both HBV and HCV at same time, but progression to HCC is increased.

- Alcohol use in patients with HCV
  - Enhances replication of HCV.
  - Accelerates progression to cirrhosis and HCC.
- Genotypes
  - Genotype 1 and greater risk of cirrhosis and death.